STUDIES OF THE RELATIONSHIP BETWEEN MUCOSAL CHANGES OF SURGICALLY RESECTED STOMACHS AND THE POLAROGRAPHIC PROTEIN WAVE IN GASTRIC JUICE

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by

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I) INTRODUCTION

A bright future for cancer teratment has now been predicted by the recent remarkable progress in the methods for early detection such as gastroscope, gastrocamera and cytologic diagnosis supported by mass x-ray examination.

However, except for the determination of gastric acidity, few cancer detecting-methods with gastric juice have been developed as clinical tests.

Changes in gastric acidity have been reported by many investigators[1~10] among the studies on the biochemical changes of the gastric juice associated with the pathological changes of the gastric mucosa, but there have been only a few reports [13,15,24~30] on the chemical changes in the protein content of the gastric juice, due to the difficulty of collecting juice free from the many contaminating factors.

Since MARTIN[11] discovered "gastroglobulin" in the acetic acid or acetone precipitates, studies on the dissolved protein in gastric juice have been made by BABKIN and WEBSTER 1931, by WEBSTER and KOMAROV 1932[12] and by MEYER et al.

Recently GLASS and BOYD[13~16] issued chemical and clinical reports on the three dissolved components, mucoprotein, mucoproteose and visible mucus.

Their origin and quantitative relationship to stomach diseases were investigated clinically.

In 1956 SASAI[18~22] found evidence of the existence of a lower molecular protein, which was later named gastric peptide, with high polarographic activity in the supernatant fluid of acetone which was discarded in the GLASS method. In his biological study, an anemic reagent and a shock reaction for rabbits were presented, and this peptide fraction was belived to be closely related to the K. I. K. factor.[23]

The polarographic patterns of the gastric juice of stomach cancer were approximately divided into three types, according to the ratio of the total wave height of gastric juice to that of the peptide fraction, and in general, the P.P.W. (polarographic protein wave) of cancer showed marked elevation as compared with the non-cancer group.

For the early diagnosis of cancer, the P. P. W. in the gastric juice was studied

by KAKEI.[62]

The author has studied the relationship between the histological findings of surgically resected stomach specimens and the P. P. W. of the gastric juice in order to examine the diagnostic value of his study.

Moreover, the physiological and the pathological aspects of this gastric peptide was experimentally examined in pure gastric juice from gastric pouch-dogs.

II) MATERIALS AND METHODS

1) Pathological examination of the surgically removed stomach

The stomach was usually opened along the great curvature and after macroscopic study strips 2 - 3 cm in length were cut from three areas; one from the tumor or the crater-edge (c) one from the pylorus (p) and one from the fundus (f) (Fig. 1).

These strips were fixed immediately in 10% neutral formol solution or CARNOY' solution and were embedded in paraffin and stained with MAYER' hematoxylin-eosin stain, van GIESON stain, and the PAS reaction according to LILLIE's method.

The metachromatic procedures of ONO's 0.05% Toluidine blue method and FEYRTER's thinone method were used in the histochemical study.

The number of surgically removed specimens were as follows;

gastric cancer—70. peptic ulcer—33. duodenal ulcer—17.
primary chronic gastritis—22. leiomyoma—1. reticulosarcoma—2.
gastric polyp—3. total cases—148.

Fig. 1 Surgically resected stomach-specimen

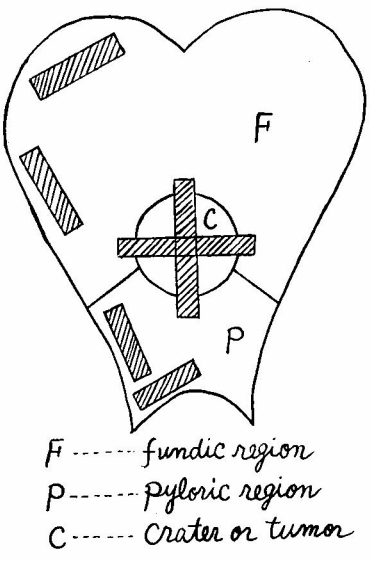
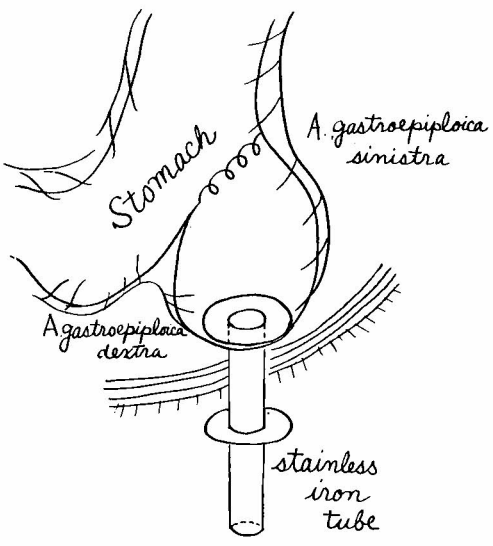


Fig. 2 Gastric pouch



2) Gastric pouch dogs

2 dogs, male and female, approximately 8 kg in weight were used for the experiment. The gastric pouch was made without any injury to the vessels or nerves as shown in Fig. 2.

3) Gastric acidity ;

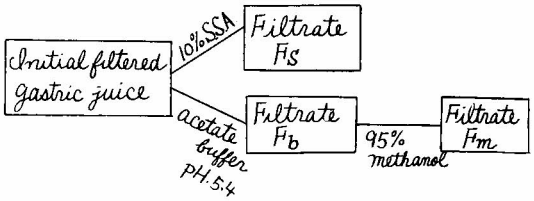
Gastric juice, aspirated through a REHFUSS tube before and after a caffeine test meal, was cleared by filtration and centrifugation and both specimens were examined in parallel.

The acidity of gastric juice was determined by the routine method of TÖPFER and classified into hypo-, normo- and hyperacidity with units of free hydrochloric acid 1-19, 20-39, and above 39, respectively.

4) P. P. W. in gastric juice studied by Dr. KAKEI

The outline is illustrated in Table 1. 1.5 ml of cleared gastric juicc was mixed with equal volumes of 10% sulfosalicylic acid and filtered after 15 minutes. The filtrate was called by Dr. KAKEI Fs fraction (sulfosalicylic acid filtrate fraction). Similar to the above, Fb (buffered gastric juice fraction) was prepared by the addition of an equal volume of acetate buffer pH5.1 To 1.0ml of Fb was added three parts of 95% methanol and this was airtightly stoppered and kept at room temperature overnight.

Table. 1



Then, the precipitants were removed by centrifugation (rpm. 3000) for 10 minutes. This filtrate was called Fm (methanol filtrate fraction). Into three electrolysis cells was poured 5.0ml each of test solution for the protein-wave analysis, the composition of these being follows;

0.001. M Cobaltic complex salt (luteosalt)
1N NH_4Cl and 1N NH_4OH in buffer solution

To these were added 0.1ml Fb and Fs, and 0.3ml Fm respectively.

Then 0.5ml methanol was added to Fb and Fs, and 0.3ml methanol to Fm so that the final volume dilution of original gastric juice in each cell was nearly the same dilution (1/112).

As soon as this was over, the polarograms were taken immediately from -0.8 to -2.0 V under constant temperature of 20°C; the sensitivity of the galvanometer was 1/100.

The protein wave was measured in terms of mm. from the diffusion current of cobalt to the 2nd maximum at approximately -1.8V.

III) OVER-ALL OBSERVATION AND CLASSIFICATION OF THE P. P. W. IN GASTRIC JUICE AND THE HISTOLOGICAL FINDING OF THE GASTRIC MUCOSA

a) P.P.W. and its classification

According to Dr. KAKEI among the heights of P. P. W., the Fb value was the highest, next the Fs value and then the Fm value. In most cases the protein waves of the fasting juice were much higher than those after a caffeine test meal, although both values are intimately related. The wave height of Fb was roughly inversely proportional to the acidity, whereas that of Fm gradually increased and then it decreased in association with the hyperacidity.

The wave height tended to increase in the presence of cancer. The gastric juice specimens were classified into the following 3 types with regard to the values of Fb and Fm.

Namely, Type I —Fm value over 25mm.
Type II —Fm value below 25mm, and Fb value over 20mm.
Type III—Fm value below 25mm and Fb value below 25mm.

With regard to type I, carcinomatous patients had higher Fm values than did the control group, while with regard to type II, carcinomatous patients gave higher Fb than did noncarcinomatous cases. In both groups, particularly in cancer the presence of the free hydrochloric acid of gastric juice was closely related to the above polarographic type; type I are acidic whereas tyep II are anacidic. The details will be reported by Kakei elsewhere.

b) Histological findings of the gastric mucosa and their classification

Many pictures of atrophic gastritis were observed. In general, the glandular atrophy is accompanied with extension of the superficial epithelial pits to the layer of muscularis mucosae. Then the superficial epithelial pits change from the gastric type to the Lieberkühn-like type with Paneth cells and goblet cells. (intestinal metaplasia). The fibrosis and the thickning of the muscularis mucosae causes thinning of the mucosa. From this point of view, gastritis is classified as follows.

A. non-glandular atrophy
   1. hypertrophic gastritis with marked thickening of the mucosa due to hyperplastic glandular elements.
   2. superficial gastritis with cellular infiltration or edema in the propria with slight or no glandulr atrophy. For example, Fig. 3 of the fundic region and Fig. 7 of the pyloric.

B. mild or moderate glandular atrophy with hyperplasia of superficial epithelial pits.
   3. mild or moderate glandular atrophy, Fig. 4 in the fundic and Fig. 8 in the pyloric region.
   4. severe glandular atrophy with most glandular elements diminished and replaced with the extended epithelial pits or with the metaplastic epithelium. For example, Fig. 5 in the fundic and Fig. 9 in the pyloric region.

C. severe glanduar atrophy without hyperplasia of the superficial epithelial pits. On account of the hyperplasia of the fibrous tissue or cellular infiltration, most

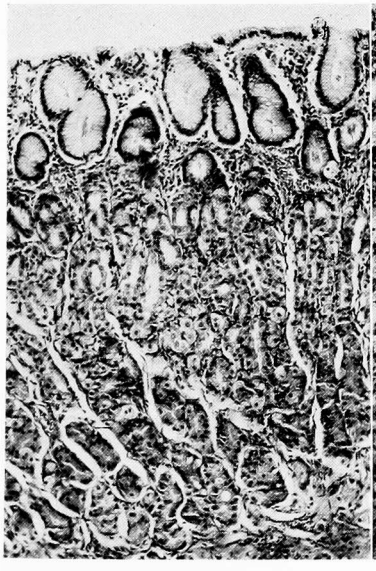


Fig. 3. type 2. in the fundic region.

Fig. 4. type 3. in the fundic region.

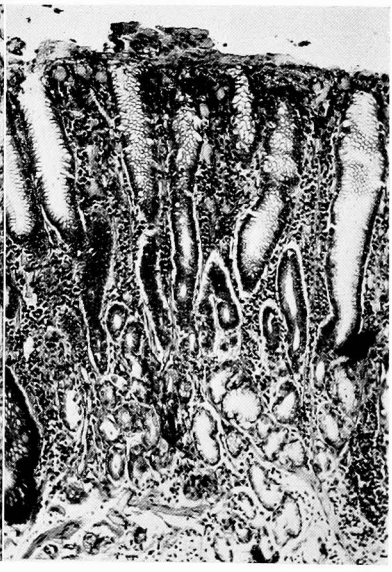


Fig. 5 type 4. in the fundic region

of glandular elements vanish. Moreover, the superficial pits show no hyperplasia. The mucosa is very thin. For example Fig. 6 in the fundic and Fig. 10 in the pyloric region.

Intestinal metaplasia was found in many speciemens. When this lay scattered in only a few pits, it was considered negative.

Fig. 6. type C. in the fundic region.

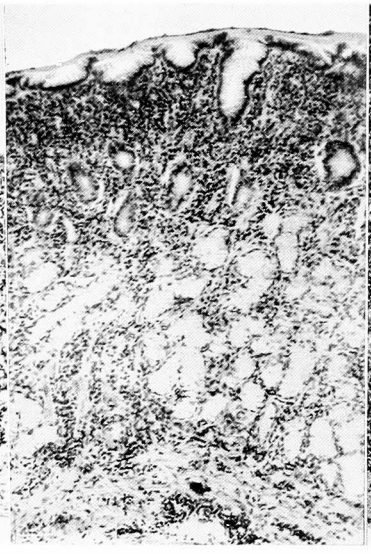


Fig 7. type 2. in the pyloric region.

Fig 8. type 3. in the pyloric region.

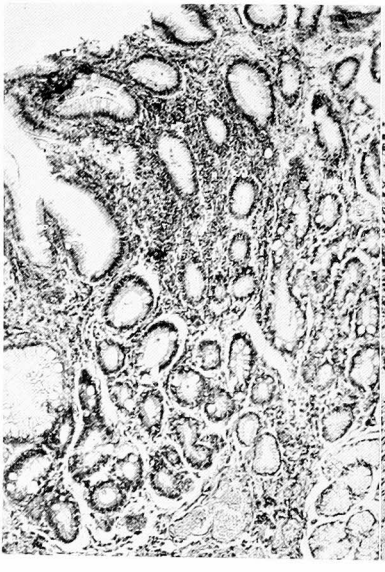


Fig. 9. type 4. in the pyloric region.

Fig. 10. type C. in the pyloric region.

IV) RESULTS

1) Age, gastric acidity and distant mucosal-change in the cancer group as compared with the control-group;

a) The distribution of the ages and case numbers of the examined patients are illustrated in Table 2. The ages of the cancer group were higher than those in the control group.

b) Achlorhydria seemed to indicate mucosal atrophy, and it was closely related to the age. The frequency of achlorhydria increased with age. About 70% of the cases over 60 years old had achlorhydria.

Table 2. Incidence of the age and cases of the surgical removed specimens.

Group	Age		Cases		
	years range	mean	total	male	female
duodenal ulcer	20 — 55	36.2	17	16	1
gastric ulcer	22 — 70	48.3	33	23	8
primary gastritis	24 — 61	49.5	22	14	7
stomach cancer	27 — 78	58.6	90	52	38

Fig. 11 Frequency of achlorhydria releted to the age.

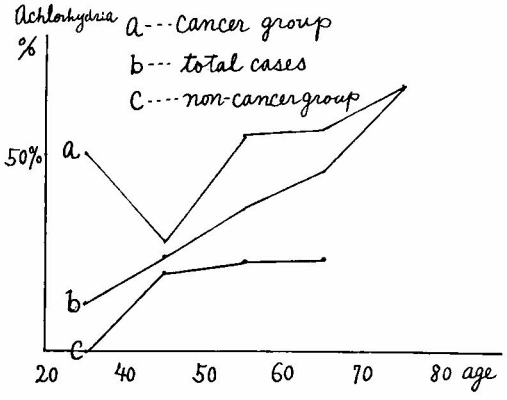
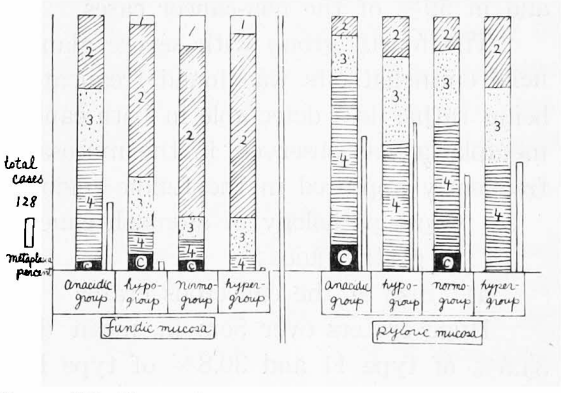


Fig. 12 Microscopic finding in the fundic and pyloric region refered to gastric acidity.



The cancer-group had a higher rate than did the others.

c) Acidity and mucosal atrophy. The degree of atrophic change in the fundic region was proportional to the gastric acidity, but in the pyloric region it was less marked. Intestinal metaplasia in the pyloric region was present more frequently than in the fundus, and was more frequent in anacidic mucosa than in acidic. Most of the cases of intestinal metaplasia in the fundic region were associated with anacidic gastric juice.

d) Intestinal metaplasia in relation to age; Intestinal metaplasia was closely related to acidity and mucosal atrophy, and increased with age (Fig. 3) 47% in the 50-60 age group and 83% in the 70-80 age group.

e) Comparative observations of histological changes of the distant mucosa in cancerous and non-cancerous stomachs.

Fig. 13 The frequency of intestinal metaplasia in the pyloric region related to the age.

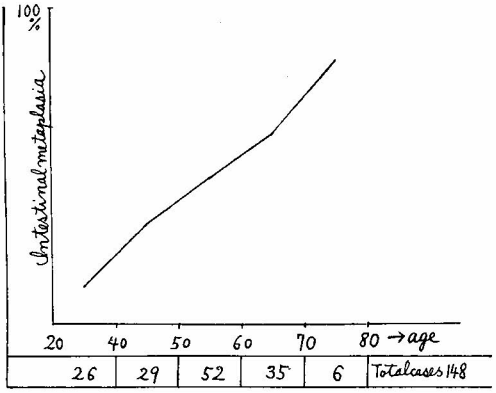
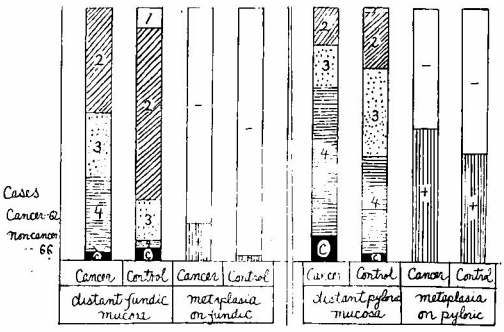


Fig. 14 The changes of the gastric mucosa in the fundic and pyloric region situated distant from the focus.



Cancer appeared more often in old age, and often in achlorhydry stomachs.

This suggested that more severe atrophy of the mucosa and more frequent occurrence of the intestinal type of mucous cells would be found in cancerous stomachs than in non-cancerous in mucosa at a distance from the sites of gastric lesions (Fig. 14). Superficial or hypertrophic gastritis in the fundic region was observed in 41% of cancer cases and in 76% of non-cancer cases, in the pyloric region absence of severe glandular atrophy was observed in 32% of the cancer cases and in 59% of the non-cancer cases.

The fourth group with severe glandular atrophy and hyperplasia of the superficial epithelial pits was found frequently in cancerous stomachs, the C-group change being rather less detectable in both cancerous and noncancerous stomachs. Intestinal metaplasia was observed in the mucosa of groups 3 and 4 (80% in group 4), and frequently appeared in the fundic region in cancer cases.

2) Gross pathology of stomach cancer in relation to polarographic protein waves in gastric juice;

a) Size of the cancerous crater

Huge craters over 5cm in mean diameter were present in 42.9% of type 1, 34.5% of type 11 and 30.8% of type III (Fig. 15).

Fig. 15 Size of cancerous crater refered with P.P.W.

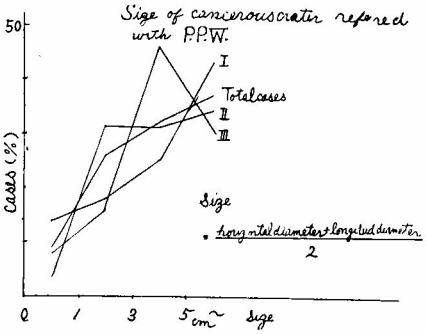
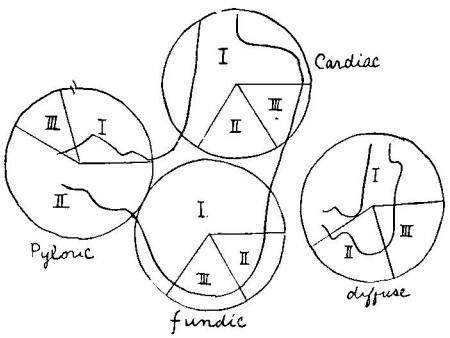


Fig. 16 Site of crater or tumor refered to polarographic pattern.



b) Site of the cancerous crater

There was a marked difference in the site of the craters between types I and II. In 25 of 29 type II cases cancerous craters were situated in the pyloric region, whereas about half of 28 type I cases had their craters in the fundic, or in the cardiac region, or sometime were so great as to cover almost the entire stomach. The distribution of craters in type III was similar to that in type I.

Table 3 Gross type (Borrmann type) refered to polarographic pattern.

Borrmann	Cases	percent	Polarogramm		
			I	II	III
I	2	2.9	0	0	2 (15.4)
II	34	48.6	10 (35.7)	20 (69.0)	4 (30.8)
III	23	32.9	11 (39.3)	8 (27.6)	4 (30.8)
IV	11	15.7	7 (25.0)	1 (3.4)	3 (23)
total	70	100	28 (100)	29 (100)	13 (100)

c) BORRMANN's classification

According to BORRMANN's[36] typing, tumors of type I according to the P. P. W. were classified as localised, 35.7% (BORRMANN's types I and II) and as infiltrative, 64.3% (BORRMANN's types III and IV). Whereas tumors of type II according to the P.P.W. were 69% localised and 31% infiltrative. (In Fig. 16 and table 3).

3) Histological examinations

a) Histological examinations of cancer

The author divided the cancer types into two groups; the differentiated cancer group as adenocarcinoma, and the undifferentiated group as carcinoma simplex.

The 54.2% of type I according to the P.P.W. was undifferentiated, whereas 68 % of type II and 70% of type III was adenocarcinoma. The relationship between intestinal metaplasia of the mucosa distant from the site of the lesions and these two cancer groups is shown in tab. 4. Severe or moderate intestinal metaplasia occurred in 52% of the carcinoma simplex group.

b) Change in mucosa distant from the site of gastric lesion

The histograms in Fig. 17. indicate the relationship between the histological finding of the mucosa distant from the site of gastric lesions and the P. P. W. of gastric juice in the cancer and non-cancer groups. In the cancer group, mucosal atrophy of the fundic region was least in the type I P.P.W.. Type II was more

Table 4. microscopical findings of cancer and intestinal metaplasia refered to Polarographic pattern

	Cancer type	Cases	total	Polarogramm			Intestinal metaplasia	
				I	II	III	none	marked
A	adenocarcinoma	32	37	11	17	9	8 (21.6%)	29 (78.4%)
	adenoc + slight mucoid	1	(59.7%)	(45.8%)	(68%)	(69.2%)		
	adenoc + C. simplex	4						
B	C. simplex	11	25	13	8	4	12 (48.0%)	13 (52%)
	scirrhus	3	(10.3%)	(54.2%)	(32%)	(30.8%)		
	mainly mucoid. c	11						
			62(100%)	24(100%)	25(100%)	13(100%)		

atrophic than type I, and intestinal metaplasia was observed in 24% in the fundic region. Type III was the most atrophic, the C group with thin mucosa being about 20%.

Similar relationships were also found in the pyloric mucosa.

In the non-cancer group, no significant difference in the histological findings of the mucosa was observed between type I and type II, but the atrophic change of the mucosa of type III was marked as compared with the mucosa of type I and type II. The fundic mucosal changes in both types I and II were slight, but intestinal metaplasia was more often observed in the pyloric mucosa in type I (50%) than in type II (37%).

c) Comparison of peptic and duodenal ulcers with regard to the findings of the pyloric and fundic mucosa and the P.P.W.;

According to Dr. KAKEI, the values of the methanol filtrate fraction decrease at a given point of acidity.

The duodenal ulcer cases show hyperacidity, but have a low value of methanol filtrate fraction. On the other hand, the peptic ulcer cases show the inversed relation. In order to clarify the meaning of the polarographic differences found by Dr. KAKEI, comparative studies were made on the mucosal change in the pylorus and fundus in peptic and duodenal ulcer. Some interesting results are shown in Fig. 18.

Fig. 17 microscopical finding of the mucosa distant from the site of gastric lesion refered to P.P.W.

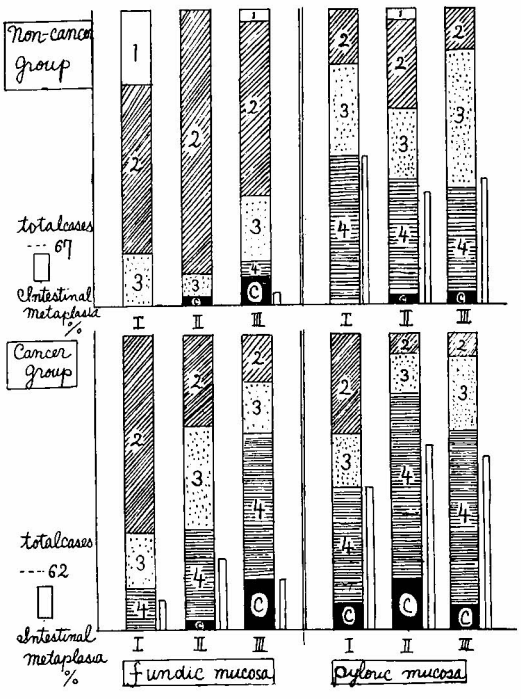
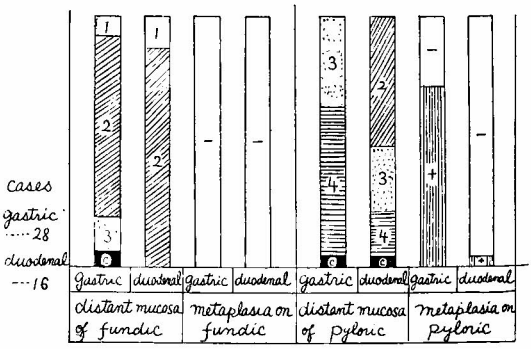


Fig. 18 microscopical finding of the mucosa distant from peptic and duodenal ulcer



The mucosal atrophy in both the pyloric and fundic regions in stomachs with peptic ulcer was more severe than in those with duodenal ulcer. Atrophic changes in the fundic mucosa were scarcely observed in cases of duodenal ulcer.

Intestinal metaplasia in the pyloric region was seen in 72% of the cases of peptic ulcer, but in none of those with duodenal ulcer.

COMMENT

KAKEI's polarographic patterns of gastric juice are closely related to the present histological findings of cancer. In addition, mucosal atrophy such as intestinal metaplasia is also related to the cancer types.

On examination of the mucosal changes found in portions distant from the site of cancer, the author concluded that in the cancer group type I P.P.W. showed less atrophic mucosa than the others, and type II had conspicuous atrophic mucosa with intestinal metaplasia involving the fundic region and type III had severely atrophic mucosa.

In the non-cancer groups, such relationships were not evident, because type I and type II in the non-cancer groups did not show the typical relationship between the buffered juice fraction and the methanol filtrate fraction. The polarographic pattern of peptic ulcer differed from that of duodenal ulcer. The author's opinion is that the secretion or the product of this intestinal metaplastic mucosa or the goblet-cell is digested by HCl and pepsin resulting in an increase of gastric peptide.

The polarographic patterns were changed with the state not only of the fundic but also of the pyloric mucosa distant from the site of gastric lesion.

4) Histochemical examination of stomach cells using carbohydrate-staining.

The dissolved proteins except in the methanol filtrate fraction in gastric juice have polysaccharide as the prosthe-

Table. 5 Histochemical finding of gastric mucosa by carbohydrate staining.

Staining method / Cell	PAS. reaction		Metachromasia with Thionine	Metachromasia with 0.05% Toluidine Blue		
				pH 2.0	pH 4.1	pH 7.0
Chief cell	−		−	−	−	−
Parietal cell	−		−	−	−	−
mucus neck cell	+		+	−	−	−
pyloric gland cell	+		+	−	−	−
superf. epith. cell	+		−	−	−	−
goblet cell	+		+	+	+	+
mucoid cancer	+		+	+	+	+
adenocarcinoma	± or		−	−	−	−

Fig. 19. PAS staining of pyloric gland, mucus, pyloric gland cell, and goblet cell as positive.

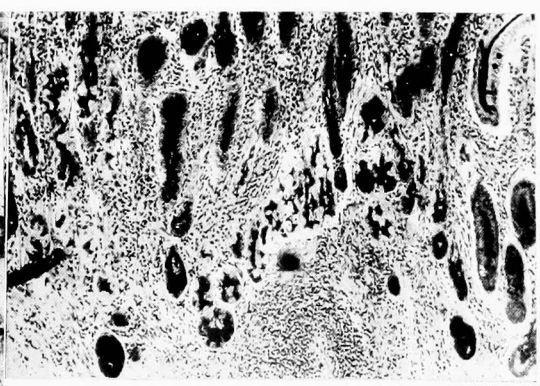


Fig. 20. PAS staining of fundic gland. mucus, superficial epithel cell, mucus neck cell as positive, partly pseudo-pyloric gland formation.

Table 6. Some interesting cases refered with polarographic diagnosis

No.	Age	Sex	Since	Chief Complaint	Tumor	X ray	Gastric Acidity	Clinical diagnosis	Polarogramm Fb	Fm	Pattern	Final diagnosis
1	43	우	3 year	epigastralgia	−	D	hyper-	polyp cancer	16	13	Ⅲ	peptic ulcer
2	61	좌	7 month	hematemesis	−	−	hyper-	cancer	25	11	Ⅱ	peptic ulcer
3	59	우	7–8 y	epigastralgia emaciation	−	−	hyper-	cancer	24	24	Ⅱ	peptic ulcer
4	50	우	3 y	epigastralgia tumor	+	D	anacid-	cancer	31	9	Ⅱ	leiomyoma
5	61	우	3 m	epigastralgia	+	−	anacid-	cancer	12	7	Ⅲ	gastritis
6	55	우	3 m	epigastralgia vomiting	−	N	hyper-	peptic ulcer	44	43	Ⅰ	cancer
7	65	좌	3 m	epigastralgia	−	N	normo-	peptic ulcer	35	28	Ⅰ	cancer

Xray——D…defect, N…niche

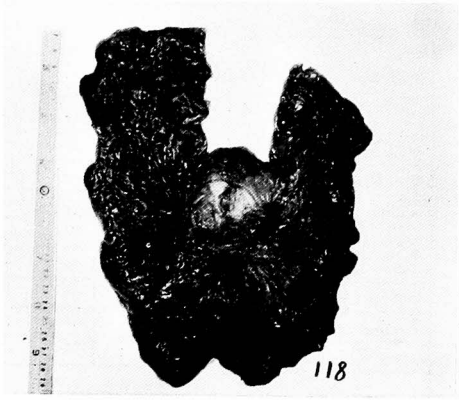


Fig. 21. Case 1. Macroscopical finding ; round ulcer with flat edge in the cardiac region.

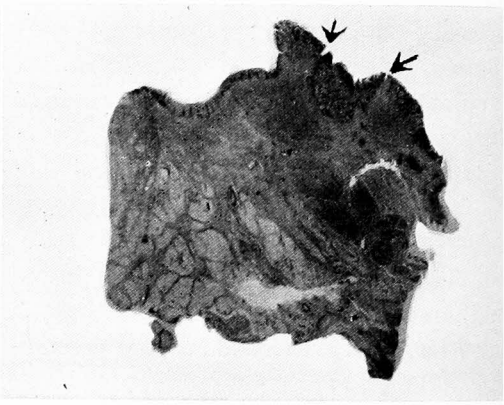


Fig. 22. Cross section of its ulcer. Arrow indexes the focus of the precancerous mucosa (case 1).

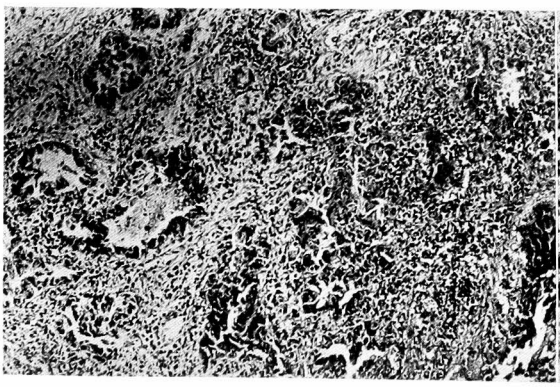


Fig. 23. Microscopical finding of the precancerous mucosa (case 1).

Fig. 24. Microscopical finding of the fundic mucosa distant from the ulcer : severe glandular atrophy with intestinal metaplasia was observed. (case 1).

tic group.

If this methanol filtrate fraction results from the digestive product of the dissolved proteins, carbohydrate staining is an important way of approaching the question of its origin.

Table 5 shows some results of carbohydrate staining. Among the various cells of the gastric mucosa, mucus neck cells, pyloric gland-cells, superficial epithelial cells, goblet-cells, mucoid cancer cells and some cells of adenocarcinoma are stained positive by the PAS reaction.[32,33] The mucus neck cells gradually form pseudopyloric glands while the chief and parietal cells decrease (Fig. 20), and their stainability with the PAS reaction is similar to that of the pyloric gland, as shown in Fig 19 and 20.

In the inclusion-staining of thionine by the FEYRTER[31] method, metachromasia occurs similarly in the pyloric gland cells and in the mucus neck cells. But metachromasia with 0.05% Toluidine blue staining[34] is negative in both.

The appearance of the stained mucus neck cells which GLASS considered the secretion of the dissolved mucoprotein is similar that of the pyloric glands in the carbohydrate-stain.

5) Some interesting clinical cases diagnosed by P.P.W.

Table. 6. shows some interesting cases among the 148 cases histologicaly examined. The first 5 cases were clinically diagnosed as stomach cancer, but after gastric resection they were confirmed as non-malignant. The clinical diagnosis in the last 2 cases was peptic ulcer, but cancer was found at operation.

The former cases did not give a high protein value. But P. P. W in the last cases suggested malignancy. Precancerous change in the mucosa was detected in 3 cases and their case histories, the clinical examinations and the histological findings are briefly described as follows.

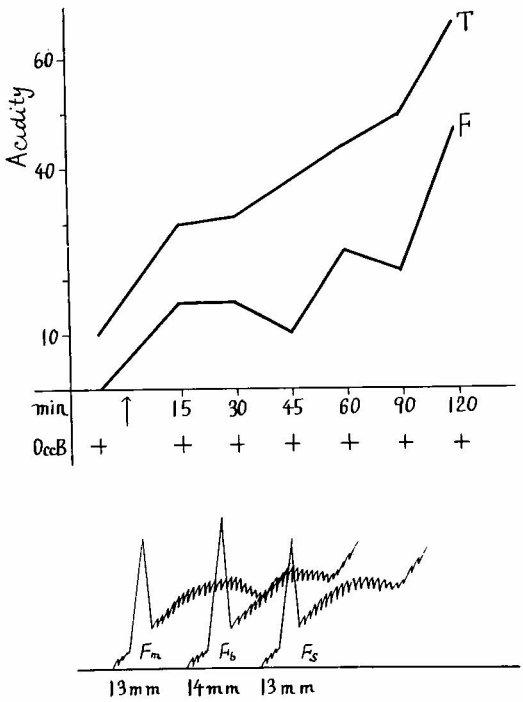
Case 1, A 52-year-old male, had suffered from epigastric pain for 5 years. 3 months before admission, severe pain occurred after heavy drinking.

Clinical examinations were as follows: No anemia, palpable tumor, cardiac niche on X-ray examination, occult blood in stool, normal gastric acidity, Fb value in polarogramm — 14 Fm value — 13, type III P.P.W., histological findings are shown in Fig 21, 22, 23 and 24.

Case 2. A 57-year-old male suffered from epigastric pain after eating. In spite of medical treatment pain increased.

Clinical examinations were as follows: No anemia, tumor was not palpable, niche

Fig. 25 Case 1



in fundus on X-ray examination, normal gastric acidity, Fb value in polarogramm--37, Fm value—25, type I. P. P. W., The gross pathology and histological findings are shown in Figs 26, 27 and 28.

Case 3. A 59-year-old male, had suffered from dull epigastric pain for 4 years. Clinical examinations were, no anemia, tumor was not palpable, some resistance in epigastrium, normal gastric acidity, polarogramm Fb—37, Fm—21 type II. The histological findings are shown in Fig. 29 and Fig. 30.

6) Experimental studies on the polarographic protein wave of gastric pouch dogs

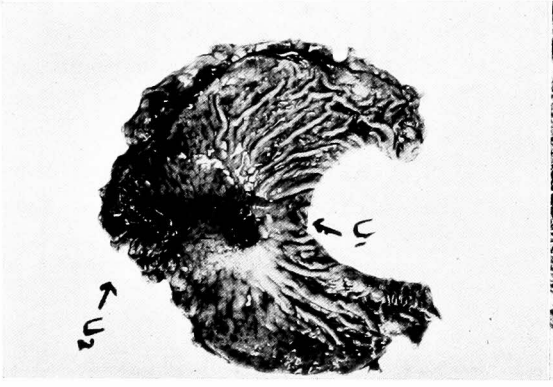


Fig. 26. Macroscopical finding (case 2) papillary upheaveled change of the pyloric mucosa and ulcer-edge.

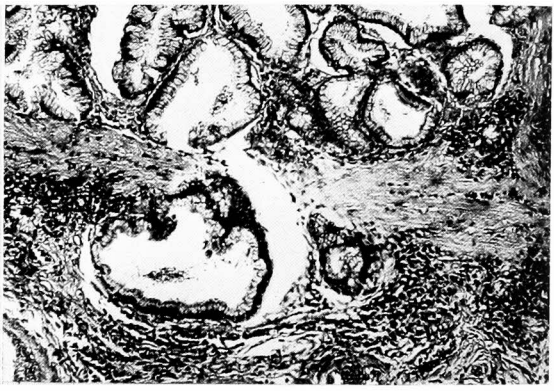


Fig. 27. Microscopical finding of the ulcer-edge of case 2. The hyperplasia of superficial epithelial cell through muscularis mucosae is observed.

Fig. 28 Case. 2

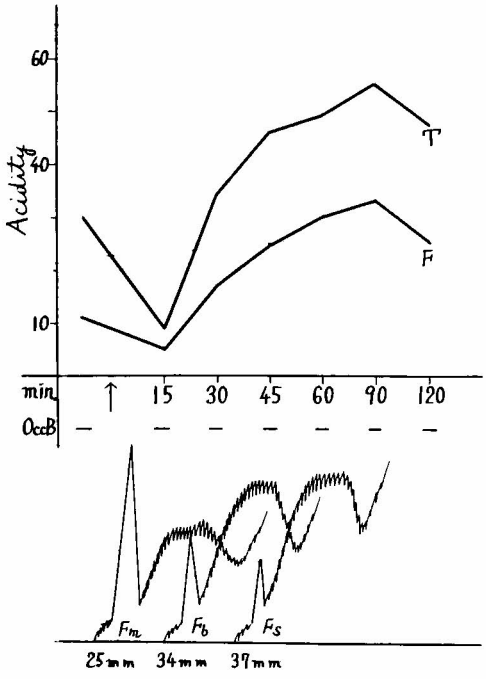
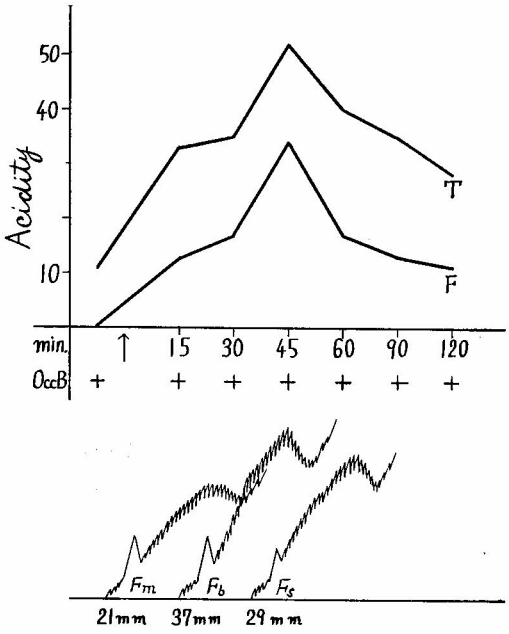


Fig. 29. Microscopical finding of the precancerous mucosa (case 3). Cystic formation of the superficial epithelial pits is characteristic.

Fig. 30 Case. 3



a) Polarographic changes after operation are shown in Fig. 31, the P.P.W. being high until 3 weeks after the operation. This might be partly due to the bleeding in gastric juice, thereafter the wave height gradually decreased, and it became constant after 2 months.

b) The influence of histamine-stimlation on the gastric juice is shown in Fig. 32. The gastric acidity and volume of secretion increased after injection, whereas the polarographic value in gastric juice rather decreased.

c) The influence of insulin-stimulation on the gastric juice is shown in Fig. 33. The gastric acidity and volume of secretion increased after 10 minutes. The wave height of P. P.W. increased 10 minutes after injection, then it decreased.

e) The influence of experimental ulcer formation on gastric juice is

Fig. 31 Polarographic changes after the operation.

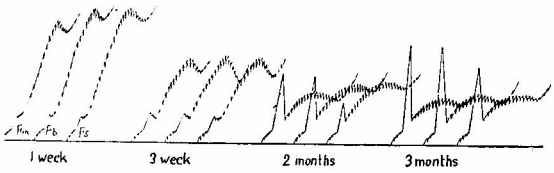


Fig. 32 Influence of histamin-stimulation on the gastric juice.

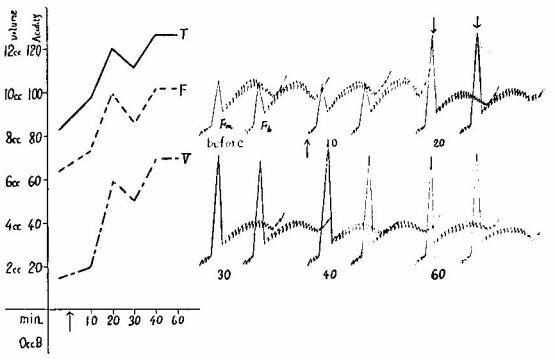


Fig. 33 Influence of the insuline-stimulation on the gastric juice.

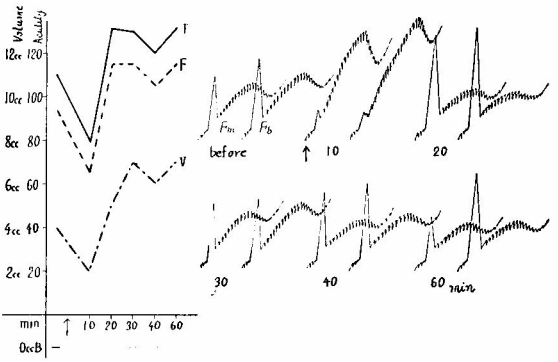
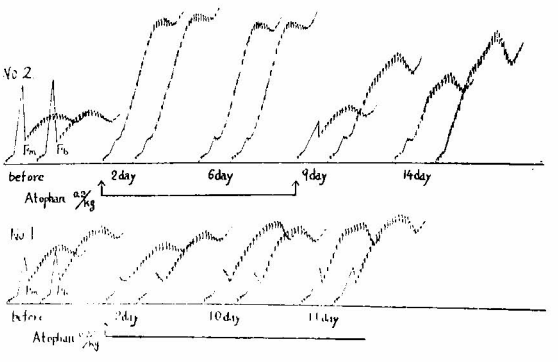


Fig. 34 Change of the polarogram after the ulcer-formation.



shown in Fig. 34. Using MALKIMANS method,[63] Atophan (Atophanyl, as manufactured name, containing Na-2-phenyl chinolin-4-carbonic 500 mg) of 0.2/kg was injected intramuscularly every day for about 10 days. The ulcer of the No. 2 dog is shown in Fig 35.

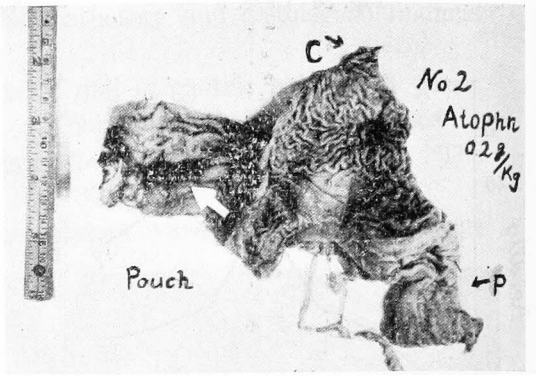


Fig. 35. Ulcer of the gastric pouch (arrow indexes) of No. 2. C…cardia. P…pylorus.

The polarographic-protein wave-height of 2 dogs, as the ulcer was produced, gradually increased. In the No. 2 dog, bleeding into the gastric juice occurred 2 days after the initial instillation, then it became severe. After 6 days, the injection was stopped, but the elevation of the protein value particulary of Fb. fraction continued, 2 weeks later, the protein value was still high.

In the No. 1 dog, though less marked than No. 2, a definite rise in the protein value could be observed.

It was interesting that experimental ulcers occurred only in gastric pouch dogs.

V) DISCUSSION

The polarographic protein wave was orginally described by R. BRDICKA[54] in 1933, and has served as various tests for cancer.

Its utilization for the studies on gastric protein has been recently reported by WADA,[50~52] SASAI[18 22] et al.

Very little[24~30] has been known about the changes in gastric protein associated with the pathological changes in the gastric mucosa, although the relationships between the gastric acidity and the mucosal changes have been reported by many investigators,[2,3,5~10] as they are closely connected with each other. Nowadays it is widely known that both the numerical change of parietal cells in the fundic gland and the gastrine secreted by the pyloric gland are main factors in deciding gastric acidity.

More extensive and severe atrophy of the mucosa is observed in gastric cancer than in other diseases, as has been reported in other studies.[40,41,45] Achlorhydria is more frequent in gastric cancer.

In regard to the change of the protein content in gastric juice due to gastric acidity, G. B. GLASS described that among the three main components of human gastric mucin freed from the trichlor acetic acid precipitate, mucoprotein is periodically secreted by the mucoid-cells in proportion to acidic secretion and probably plays a role as a buffer or vehicle for hydrochloric acid, and shows a relatively high value in the fasting gastric content of the juvenile, hyperacid, irritable stomach, of duodenal ulcer, and of some cases of hyper-or normoacid gastritis.

The dissolved mucoproteose, on the other hand, seems to be a product of surface epithelium and originates from the enzymatic digestion of the surface epithelium

mucus, and is a constant component of the gastric contents and its presence is not related directly to the secretion of acid and the highest values are found in anacidic fasting fluid.

As for the gastric peptide in the present problem, it has already been reported by SASAI and co-workers[18~22] that in the presence of HCl mainly when hypoacid one, peptide has a high level. According to the experimental study of KAKEI, the peptide value strikingly increases after digestion by anacid gastric juice.

In general, severe mucosal atrophy is observed in type III representing a marked decline in all protein-wave values regardless of the presence or absence of cancer, but such observations are not always justified, because the dilution of the protein contents by a caffeine test solution may interfere with pyloric passage.

But a significant difference is found between the mucosal changes in type I P. P.W. and that in type II P.P.W.

In short, the differences in the protein content in gastric juice of cancer are influenced by the site of the tumor and the spreading activity over the wall rather than by the size of the crater or tumor.

The histological difference in cancer is important in the protein pattern in gastric juice, and it is closely related to the mucosal change distant from the tumor.

In type I, almost half the tumors are situated in the fundus, or cardiac area or extend over the whole stomach, and spread infiltratively. The great majority of tumors were of the carcinoma simplex type, and no marked mucosal atrophy was found in portions distant from the tumor particularly in the fundus.

In type II, on the contrary, tumors were situated in the pyloric region and were the localised type of Borrmann.

In the mucosa distant from the gastric lesion severe glandular atrophy with hyperplasia of the superficial epithelial pits was observed and the mucosa was of the characteristic intestinal type.

The high incidence of the intestinal type of mucosa in adenocarcinoma and the less atrophic change of mucosa distant from in ulcer-cancer whose histological findings are mainly scirrhus has been reported by other investigators.[1,38,64]

Considering the clear cut different patterns of the polarograms, these 2 types have a different histogenesis. Type II representing adenocarcinoma may rise from chronic gastritis or intestinal metaplasia. On the other hand, type I representing carcinoma simplex or scirrhus carcinoma grows on chronic peptic ulcer.

In regard to chronic gastritis, there are different opinions about whether it is a precursor of cancer or not. According to IVY[24] the physiological change accompaning gastritis, i. e. the impairment of the mucus barrier to exogenous carcinogen, may become the precursor.

The gastritis observed in cancer stomachs has characteristic features, i. e. marked hyperplasia of the mucus secreting cells associated with glandular atrophy, as JUDD[38] previously reported.

The intestinal metaplasia described by KUPFFER in 1883 has been studied by many authors.[42,43,44,64] It appears more frequently in cancer, less often in peptic ulcer,

and least in duodenal ulcer.

Intestinal metaplasia is increasingly frequent as age progresses. STOUT's report[37] is in agreemt with the authors data.

The secretion of the mucosa with intestinal metaplasia may play a role in the protein constituents of gastric juice. The mucosal changes in type. II. P.P.W. reveals the characteristic feature of extensive intestinal metaplsia extending to the fundic region.

Therefore the secretion from the goblet-cells of the intestinal type of mucosa may be a source of protein precipitable by sulfosalicalic acid (equivalent to the dissolved mucin of GLASS).

Another evidence is interesting in the difference between peptic ulcer and duodenal ulcer from the view point of the polarographical patterns. Intestinal metaplasia is more frequently observed in the pyloric mucosa of peptic ulcer stomachs. The high peptide level in peptic ulcer may be partly related to the digestive products of this goblet-cell in HCl, since this type of peptic ulcer occurs in normo-or hypoacid stomachs.

The role of the pyloric glands has been little investigated as the source of gastric protein.[28] It is frequently observed that a high peptide value occurs in gastric juice even with diffuse infiltrative tumors except for those in the pyloric region.

The polarographic changes in gastric juice are closely related to the mucosal changes in the pyloric gland as well as in the fundus.

The mucus neck cells regarded by GLASS[14] as an important secretory cell of mucoprotein morphologically resemble the cells of the pyloric glands, and, moreover, some carbohydrate-stains have similar results in both cells.

The product of the pyloric glands may be digested by HCl and pepsin, too, and cause an increase in peptide.

Achlorhydria is more frequent in gastric cancer. According to the numerous observations by HURST[57] and COMFORT,[2,3] patients with achlorhydria have, indeed, a high possibility of developing cancer, but they question whether acidic gastric juice will be altered to anacidic when cancer occurs. In our cases, there are unexpectedly many cancers with hydrochloric acid in the gastric juice. It is interesting that the precancerous cases of peptic ulcer and the cases of carcinoma in situ among the authors cases occur in hyper-or normoacidic stomachs.

The polarographic method for the detection of cancer is especially important in these acidic cases, and the value of gastric peptide is especially signficant.

Why does the protein content with polarographical activity in gastric juice increase in gastric cancer?

This question cannot be answered at all, because the experimental observation of cancer still impossible.

The author's experiments with gastric pouch dogs indicate that the protein content, especially the gastric peptide, markedly increases in ulcer formation with atophanyl injection, while, with physiological stimulation, it decreases.

A high protein value in cancer is partly due to the absence of the ordinary

diluting activity of glandular secretion, as KAKEI[62] described.

The protein level may be markedly elevated in cancer as a result of the increased products from destroyed or regenerated mucosa due to the progress of cancer, or of the secretory change in the extensive change in the mucosa of cancer cases. The gastric peptide value will be increased by digestion with HCl and pepsin in the acidic cases.

VI) SUMMARY

1) 148 cases of surgically resected stomachs were examined histologically, and discussed in relation to polarographic protein wave as well as gastric acidity in gastric juice measured by KAKEI.

2) Decrease in gastric acidity is closely related to fundic mucosal atrophy. The presence of intestinal metaplasia caused anacidity or decreased gastric acidity.

3) The increased peptide type in gastric juice was different histologically from the increased dissolved mucin type.

The former was frequently observed in cancer of the infiltrative type described by Borrmann and situated in various regions and in the undifferentiated histological type and the slight mucosal changes distant from the tumor.

The latter was observed in cancer localized in the pylorus with the histological picture of adenocarcinoma and with mucosal atrophy and intestinal metaplasia.

4) The atrophic change of the mucosa in peptic ulcer was more severe than that of duodenal ulcer. Intestinal metaplasia in the pyloric region was more frequent in peptic ulcer.

Gastric ulcer gave a higher peptide value than duodenal ulcer.

5) Pyloric gland cells were similar to mucus neck cells in some carbohydrate stains.

6) High protein values, particularly a high peptide value, was suggestive of malignancy.

7) 3 precancerous cases were studied, and their clinical course and histological studies were reported in relation with the protein pattern of the gastric juice.

8) The experimental studies with gastric pouch dogs showed that gastric peptide had canstant constituents in pure gastric juice and that it increased in pathologic states such as ulcer formation.

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和文抄録

手術胃病理所見と胃液内蛋白像の関係について

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篠 原 秀 幸

胃液可溶性蛋白に関しGlass法では捨てられていたアセトン上清中に，笹井はポーラログラム活性の高いペプタイド分劃が存在する事を証明し，胃癌胃液で主として有酸胃液中には此のペプタイドが著増する事を発表した．本邦胃癌殊に初期の癌に於ては有酸性胃液がかなり高率にみられる所から，此等ペプタイドの起源及び他の癌反応（ニンヒドリン反応，KIK反応，トキソホルモン）との関係等の検討が，笹井，筧，久保等によつてすすめられて，而も癌の早期診断法の1つとして応用しようとの努力が試みられている．

私は外科的に切除された胃癌，胃潰瘍，十二指腸胃潰癌，胃炎等148例について病巣部及び遠隔部粘膜の病理組織所見を検し，之れと胃液酸度及び共同研究者筧によるポーラログラムを以てする，胃液内蛋白像との相関を検すると共に，胃嚢犬より得た胃液について生理的及び潰瘍作製時の変化を研究し以下の結果を得た．

1) 胃液酸度と胃底腺萎縮所見との間に密接な比例関係をみた．化生粘膜の出現したものは無酸症，或いは酸度の減少をみた．

2) 胃癌胃液にはペプタイド増加を来たすⅠ型，ズルホサリチル酸沈澱蛋白及び可溶性蛋白の増加をみるⅡ型及び全蛋白の減少を来たすⅢ型があるが，此等に対応した病理所見として，Ⅰ型にはボールマン型の滲潤型（3或は4型）で幽門域外の腫瘤が多く，周辺粘膜及び遠隔粘膜には腸腺様化によつて代表される萎縮性変化が少なく，単純癌型が多くみられた．Ⅱ型は比較的老令者に多くて幽門腺域に主病巣の限局するものが多く，腺癌がその大多数を占め，周辺及び病巣遠隔粘膜には強度の腸腺様化生がみられた．Ⅲ型では略々Ⅱ型にみられた特徴がみられるが，粘腺像で菲薄性変化が強く，ポリープ及びポリープ癌がこれに属した．

3) 胃潰瘍では十二指腸潰瘍に比べて酸度が低いのに関わらず，ペプタイドは増加する．胃潰瘍では十二指腸潰瘍に比し粘膜の萎縮性変化が強く，特に幽門部に於ける腸粘膜化生の生現は高率であつた．

非癌疾患でも癌のように3型が区別せられるがⅠ，Ⅱ型の粘膜変化には著明な差異が認められず，Ⅰ，Ⅱ型とⅢ型の間では後者に萎縮性変化が高度であつた．

4) 癌診断に利用し，癌が疑われて術後病理学的に非癌であつた5例では，ポーラログラムによる蛋白像も非癌型に属していた．

組織学上前癌性変化を認めた3例中2例ではこの検査法で癌が疑われ，他の1例では病巣遠隔粘膜に至る高度の萎縮性変化がみられた．

5) 胃嚢犬により此のペプタイドは生理的にも純粋胃液中に存し，ヒスタミンでは減少しインシュリン刺戟によつては，10分後に増加し以後むしろ減少し，アトファンによる潰瘍作製時には増加した．